REMARKS

Claims 1-51 and claims 56-59 are pending. Claims 1, 4-6, 15, 33, 36, 44, 45, 47, 49, 50, and 56-59 have been amended. Claims 7-14, 16-19, 23-32, 34-35, 39-42, and 46 have been cancelled without prejudice. Claims 52-55 have been withdrawn by the Examiner [Office Action, page 3, third full paragraph].

Applicants acknowledge election without traverse of Group II, claims 1-60 drawn to compounds and methods of use wherein G or W is a directly linked piperazinyl or morpholinyl group. As a result of the above claim cancellations and withdrawals, the following claims are now pending: compound and composition claims 1-6, 15, 20-22, 33, 36-38, 43-45, and 47-48, and method claims 50-51 and 56-59.

In addition to changing the dependencies of certain claims, the amendments include the following.

Claim 1 was amended to exclude non-elected subject matter. Support for adding the terms "piperazinyl or morpholinyl" in the definition of W can be found in original claim 1, where W can be a C 1-8 heterocyclyl, and the specification on page 11, line 33 and page 12, line 3.

Claims 4-6 were amended to replace "G" with -W-; support can be found in original claim 1, where one of R1, R2, and R3 is G or W. Similarly, claim 15 was amended to replace "Q" with -W-.

Claims 44 and 45 were amended by deleting compounds not within the elected subject matter.

Claims 47, 49, and 50 were amended to change the dependencies.

Claims 51 and 58 were amended to delete "(predementia)" with the understanding that mild cognitive impairment includes predementia.

Applicants respectfully request reconsideration of the pending claims in view of the above amendments and remarks below.

Objection

Claims 1-51 and 56-59 were objected to for containing non-elected subject matter [Office Action, page 3, fourth full paragraph]. Applicants have cancelled claims 7-14, 16-19, 23-32, 34, 35, 39-42, and 46 without prejudice and amended claims 1, 4-6, 15, 33, 36, 44, 45, 47, 49, 50, and 56-59 to overcome this objection.

Claims 47-49 and 56-59, now amended to overcome the above objection, had no other statutory or art-based rejections and are therefore believed to be in condition for allowance.

Rejection Under 35 USC 112

Claims 59, 51, and 50 were variously rejected.

Claim 59 was rejected for lack of enablement because "applicant does not give support for 'preventing' all forms of these disorders" (such as upper airway allergic response, nasal congestion, or allergic rhinitis) [Office Action, page 6, second paragraph]. This rejection is respectfully traversed.

While Applicants recognize that, in general, "prevention" of a disease may be more difficult to demonstrate or to believe than "treatment" of a disease, Applicants nevertheless request reconsideration for the following simple reason.

It is common practice for people with allergies or hayfever to take an antihistamine in the morning or evening. The intent and the usual result is that, for the next several hours, they will be less congested or be able to breathe more easily. In other words, congestion is prevented. It is true that commercial antihistamines may relate to a different histamine subtype than that related to the instant application. However, the point is that the kinds of congestion in claim 59 are known to be susceptible of prevention, and that such a utility is therefore not incredible on its face. (This would be in contrast, for example, to a disease such as cancer, with multiple and inter-related causes and long time delays between exposure to a carcinogen and the perceptible occurrence of a tumor, and no known preventive therapy.) Applicants respectfully submit that the data presented in the application is sufficient to support the H3 antagonism activity of the claimed compounds, and therefore supports the method of preventing upper airway allergic response, nasal congestion, or allergic rhinitis, as claimed.

As claim 59 had no other statutory or art-based rejections, Applicants respectfully submit that claim 59 is in condition for allowance.

Claim 50 was rejected for indefiniteness because the term "modulate" was used. According to the Examiner, " 'Modulate' means that a histamine H3 receptor can both inhibit and cause a disease or condition. It is unclear whether Applicant claims that the role of histamine H3 is to inhibit or to cause a disease or condition." [Office Action, page 7, second full paragraph].

To clarify, Applicants claim methods of treating an undesirable disease or condition. Applicants do not claim methods of causing undesirable diseases or conditions. The compounds of the application have been shown to modulate histamine H3 receptor, and therefore are suitable for treating disease or conditions that are affected by modulation of the histamine H3 receptor.

As claim 50 had no other statutory or art-based rejections, Applicants respectfully submit that claim 50 is in condition for allowance.

Claim 51 was rejected for indefiniteness because both "mild cognitive impairment" and "predementia" were used in a Markush group, and according to the Office Action, predementia is a narrower statement of mild cognitive impairment. Applicants have amended claim 51 and also claim 58 where similar language appears in a similar context, to delete "predementia" solely on

the basis that mild cognitive impairment is understood to include predementia.

As claim 51 had no other statutory or art-based rejections, Applicants respectfully submit that claim 51 is in condition for allowance.

In view of the remarks and amendments above, Applicants respectfully request that these 112 rejections of claims 50, 51, and 59 be withdrawn, and that these claims be allowed.

Rejection Under 35 USC 103

Claims 1-46 were rejected as unpatentable over Goto et al. (CAPLUS AN 1996:754425) in view of Greene ("Protective Groups in Organic Synthesis") [Office Action, page 4, last paragraph].

According to the Office Action, "the difference between Goto et al. and the instant claims is that Goto et al disclose an acyl protecting group on the nitrogen of the piperidine ring, while the instant claims consist of a (phenyl)C 1-6 alkyl protecting group on the nitrogen of the piperidine ring [Office Action, page 5, second paragraph]." According to the Office Action, one of ordinary skill would have been motivated to use Goto to prepare the claimed compounds because the substitution of a phenylalkyl nitrogen protecting group for an acyl nitrogen protecting group is an obvious variant [Office Action, page 5, third paragraph]. Applicants respectfully traverse this rejection.

It is not proper to combine Goto with Greene. On the one hand, Greene is a reference for chemical synthesis, a reference for chemical protecting groups. On the other hand, Goto is a reference about antioxidants, about compounds that inhibit degeneration and necrocytosis of cerebral nerve cells [Goto, claim 1, column 52]. If Applicants were claiming a chemical process, then it might be proper to cite Greene, since the chemical synthetic similarity of one protecting group with another would be relevant in a given chemical process. However, this is not the subject matter that Applicants are claiming.

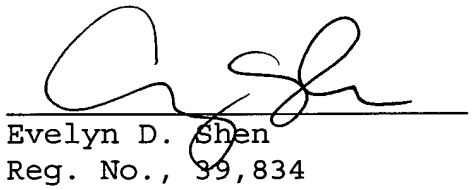
Applicants are claiming compounds and methods of using them to treat histamine H3 receptor-mediated conditions and diseases. Nothing in Green or Goto suggests that the inhibition of degeneration and necrocytosis of nerve cells is in any way related to histamine H3 receptor. Nothing in Greene or Goto suggests that a putative similarity in chemical protecting groups is in any way related to the efficacy of Goto's compounds as necrocytotic inhibitors. The Office Action has not pointed out where to find the suggestion in Greene or Goto that, in view of the structural differences between Goto and the claimed compounds, one of ordinary skill would have a reasonable expectation of both making the structural changes described in the Office Action and succeeding in obtaining a good inhibitor of degeneration and necrocystosis.

The Office Action has failed to state a prima facie case of obviousness. It is improper to combine Goto with Greene. Even if they were combined, the combination does not provide the required rationale or teaching.

For the reasons stated above, Applicants respectfully request that this rejection be withdrawn.

Applicants respectfully petition that the period for response be extended three months up to and including November 22, 2002. Please charge any fees to Deposit Account number 10-0750/ORT-1474/EDS. Three copies of this request are enclosed herewith.

Respectfully submitted,



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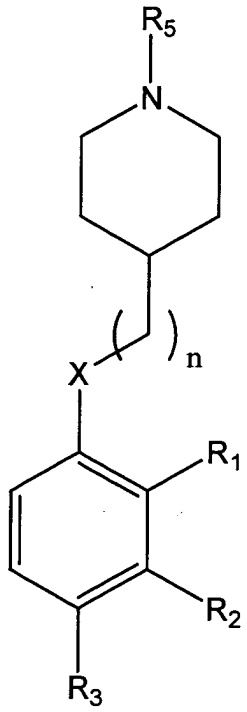
November 22, 2002

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

1. [Amended] A compound of formula (I):



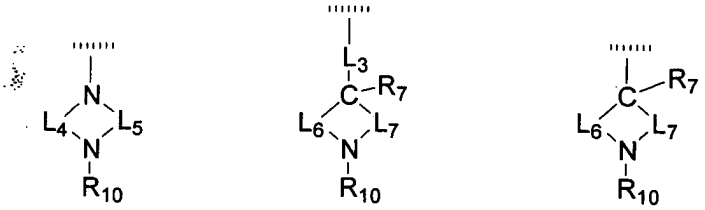
wherein X is O;

n is an integer from 0 to 3;

R_5 is C $_{1-10}$ alkyl, C $_{3-8}$ alkenyl, C $_{3-8}$ cycloalkyl, (C $_{3-8}$ cycloalkyl) C $_{1-6}$ alkyl, (phenyl)C $_{1-6}$ alkyl, (phenyl)C $_{3-8}$ alkenyl, or (C $_{1-8}$ alkylcarbonyl)C $_{1-8}$ alkyl;

one of R_1, R_2, and R_3 is [G or] W, wherein one of the remaining two is selected from H and halogen, and the third being hydrogen;

[G is a nitrogen-containing group selected from one of the following:
$-OL_1Q$, $-L_2Q$, $-N(L_1Q)R_5$, $-L_3C(L_1Q)R_6R_7$, $-C(L_1Q)R_6R_7$,



(i) (ii) (iii)

wherein:

L_1 is C $_{2-6}$ alkylene, C $_{3-8}$ cycloalkylene, C $_{4-6}$ alkenylene, C $_{4-6}$ alkynylene, C_{2-5} alkanoyl, (phenyl)C $_{1-6}$ alkylene, (naphthyl)C $_{1-6}$ alkylene, (C $_{2-5}$ heteroaryl)C $_{1-6}$ alkylene, (phenoxy)C_{1-6} alkylene, or (C $_{2-5}$ heteroaryloxy)C_{1-6} alkylene;

L_2 is C_{1-6} alkylene, C $_{3-8}$ cycloalkylene, C $_{3-6}$ alkenylene, C $_{3-6}$ alkynylene, C_{2-5} alkanoyl, (phenyl)C $_{1-6}$ alkylene, (naphthyl)C $_{1-6}$ alkylene, (C $_{1-5}$ heteroaryl)C $_{1-6}$ alkylene, (phenoxy)C_{1-6} alkylene, (C $_{1-5}$ heteroaryloxy)C_{1-6} alkylene, or (C $_{1-5}$ heteroarylthio)C_{1-6} alkylene;

L_3 is C_{1-6} alkylene, C $_{2-6}$ alkenylene, C $_{2-6}$ alkynylene, C_{2-5} alkanoyl, (phenyl)C $_{1-6}$ alkylene, phenyl, naphthyl, (naphthyl)C $_{1-6}$ alkylene, C $_{1-5}$ heteroaryl)C $_{1-6}$ alkylene, (phenoxy)C_{1-6} alkylene, (C $_{1-5}$ heteroaryloxy)C_{1-6} alkylene, or C $_{2-5}$ heteroaryl;

L_4 is C_{1-5} alkylene;

L_5 is C_{1-5} alkylene;

L_6 is C_{1-5} alkylene;

L_7 is C_{1-5} alkylene or absent;

Q is -NR_8R_9 or a non-aromatic C $_{2-15}$ heterocyclyl ring system containing at least one nitrogen atom and optionally between 1 and 3 additional heteroatoms selected from O, S, and N in each ring;]

R_6 is independently selected from hydrogen, C $_{1-8}$ alkyl,
C $_{1-6}$ alkoxy, C $_{2-8}$ alkenyl, C $_{3-7}$ cycloalkyl, (C_{3-7} cycloalkyl)C_{1-6} alkylene, C_{2-15} heterocyclyl, and (C_{2-7} heterocyclyl)C_{1-6} alkylene;

R_7 is H, hydroxyl, halo, C $_{2-6}$ alkoxy or absent where the carbon linking L_6 and L_7 (or bonded to R_6) participates in a double bond;

each of R_8 and R_9 is independently selected from hydrogen, C_{1-6} alkoxy, C_{1-8} alkyl, C_{3-8} alkenyl, C_{3-7} cycloalkyl, (C_{3-7} cycloalkyl)C_{1-6} alkylene, C_{2-15} heterocyclyl, phenyl, (C_{2-15} heterocyclyl)C_{1-6} alkylene, and (phenyl) C_{1-6} alkylene;

R_{10} is H, C_{1-8} alkyl, C_{3-8} alkenyl, C_{3-7} cycloalkyl, (C_{3-7} cycloalkyl)C_{1-6} alkylene, (C_{2-15} heterocyclyl)C_{1-6} alkylene, or (phenyl) C_{1-6} alkylene;

W is piperazinyl or morpholinyl [-CN, -CHO, halogen, C_{1-8} heterocyclyl, (C_{1-8} heterocyclyl)-O-, phenoxy, phenyl, (phenyl)C_{1-6} alkylene-O-, -C(=O)R_x, -C(OH)R_xR_y, C_{1-8} alkyl, C_{1-8} cycloalkyl, or -NR_xR_y;

wherein each of R_x and R_y is independently selected from H, C_{1-6} alkyl, C_{1-6} alkanoyl, C_{1-8} heterocyclyl, and phenyl;]

wherein each of the above alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene, heterocyclyl, cycloalkyl, and aryl groups may each be independently and optionally substituted with between 1 and 3 substituents selected from halo, amino, nitro, hydroxyl, and C_{1-3} alkyl;

[wherein substituents of Q can be further selected from carboxamide, C_{2-6} alkyl, C_{1-8} heterocyclyl, N(C_{1-6} alkyl)(C_{1-8} heterocyclyl), NH(C_{1-8} heterocyclyl), (C_{1-3} alkylene)(C_{1-8} heterocyclyl), O(C_{1-8} heterocyclyl), O(C_{1-6} alkyl), O(C_{3-6} cycloalkyl), phenyl, (C_{1-3} alkylene) phenyl, N(C_{1-6} alkyl)(C_{1-3} alkylene) phenyl, and O(C_{1-3} alkylene) phenyl where each of above heterocyclyl, phenyl, and alkyl groups may be optionally substituted with from 1 to 3 substituents independently selected from halogen, nitro, cyano, and C_{1-3} alkyl;]

or a pharmaceutically acceptable salt, ester, or amide thereof.

2. A compound of claim 1, wherein R_5 is C_{1-5} alkyl, C_{3-4} alkenyl, C_{3-6} cycloalkyl, (C_{3-6} cycloalkyl) C_1alkylene, (phenyl)C_{1-3} alkylene, or (phenyl)C_{3-4} alkenylene.

3. A compound of claim 2, wherein R_5 is branched C_{3-5} alkyl, C_{3-6} cycloalkyl, and (C_{3-6} cycloalkyl)C_1 alkylene.

4. (Amended) A compound of claim 1, wherein one of R_2 and R_3 is [G] W.

5. (Amended) A compound of claim 4, wherein R_2 is [G] W.

6. (Amended) A compound of claim 4, wherein R_3 is [G] W.

7. (Cancelled) A compound of claim 1, wherein L_1 is C_{2-3} alkylene.

8. (Cancelled) A compound of claim 1, wherein L_2 is C_{1-6} alkylene, (C_{1-5} heteroaryl)C_{1-6} alkylene, or -phenyl-C_{1-6} alkylene.

9. (Cancelled) A compound of claim 8, wherein L_2 is methylene.

10. (Cancelled) A compound of claim 1, wherein L_3 is ethylene, vinylene, ethynylene, and phenylene.

11. (Cancelled) A compound of claim 1, wherein Q is a non-aromatic nitrogen-containing C_{2-5} heterocyclyl.

12. (Cancelled) A compound of claim 11, wherein Q is selected from piperidyl, N-(C_{1-6} alkyl)piperazinyl, piperazinyl, pyrrolinyl, pyrrolidinyl, and morpholinyl.

13. (Cancelled) A compound of claim 11, wherein Q is N-morpholinyl or N-piperidinyl, optionally substituted with between 1 and 3 substituents selected from hydroxyl, carboxamide, C_{1-6} alkyl, C_{1-8} heterocyclyl, N(C_{1-6} alkyl)(C_{1-8} heterocyclyl), NH(C_{1-8} heterocyclyl), (C_{1-3} alkylene)(C_{1-8} heterocyclyl), O(C_{1-8} heterocyclyl), O(C_{1-6} alkyl), O(C_{3-6} cycloalkyl), phenyl, (C_{1-3} alkylene) phenyl, N(C_{1-6} alkyl)(C_{1-3} alkylene) phenyl, and O(C_{1-3} alkylene) phenyl where each of above heterocyclyl, phenyl, and alkyl groups may be optionally substituted with from 1 to 3 substituents independently selected from halogen, nitro, cyano, and C_{1-3} alkyl.

14. (Cancelled) A compound of claim 13, wherein Q is substituted with a substituent comprising a C_{1-6} heterocyclyl group selected from: pyridyl, pyrimidyl, furyl, thiofuryl, imidazolyl, (C_{1-6} alkyl) imidazolyl, oxazolyl, thiazolyl, 2,3-dihydro-indolyl, benzimidazolyl, 2-oxobenzimidazolyl, (C_{1-6} alkyl) tetrazolyl, tetrazolyl, (C_{1-6} alkyl) triazolyl, triazolyl, (C_{1-6} alkyl) pyrrolyl, and pyrrolyl.

15. (Amended) A compound of claim 1[4], wherein [Q] <u>W</u> is a substituted or unsubstituted N-morpholinyl.

16. (Cancelled) A compound of claim 1, wherein Q is NR_8R_9 wherein each of R_8 or R_9 is independently selected from hydrogen, C_{1-8} alkyl, C_{3-8} alkenyl, C_{3-7} cycloalkyl, (C_{3-7} cycloalkyl)C_{1-6} alkylene, C_{2-5} heterocyclyl, phenyl, (C_{2-5} heterocyclyl)C_{1-6} alkylene, and (phenyl) C_{1-6} alkylene.

17. (Cancelled) A compound of claim 16, wherein one of R_8 and R_9 is hydrogen.

18. (Cancelled) A compound of claim 17, wherein R_8 is H and R_9 is phenyl or aromatic C_{1-8} heterocyclyl optionally substituted with 1-3 substituents selected from halo, nitro, cyano, and C_{1-3} alkyl.

19. (Cancelled) A compound of claim 18, wherein R_9 is phenyl, pyridyl, pyrimidyl, furyl, thiofuryl, imidazolyl, (C_{1-6} alkyl) imidazolyl, oxazolyl, thiazolyl, 2,3-dihydro-indolyl, benzimidazolyl, 2-oxobenzimidazolyl, (C_{1-6} alkyl) tetrazolyl, tetrazolyl, (C_{1-6} alkyl) triazolyl, triazolyl, (C_{1-6} alkyl) pyrrolyl, and pyrrolyl.

20. A compound of claim 18, wherein R_5 is C_{1-5} alkyl, C_{3-4} alkenyl, C_{3-6} cycloalkyl, (C_{3-6} cycloalkyl) C_1alkylene, (phenyl)C_{1-3} alkylene, or (phenyl)C_{3-4} alkenylene.

21. A compound of claim 1, wherein n is 0 or 1.

22. A compound of claim 21, wherein n is 0.

23. (Cancelled) A compound of claim 1, wherein G is selected from:
(1) formula (i) wherein L_4 and L_5 are independently selected from C_{2-3} alkylene,
(2) formula (iii) wherein L_6 is C_{2-3} alkylene and L_7 is C_{2-3} alkylene or absent,
(3) L_2Q wherein L_2 is C_{1-6} alkylene, phenyl C_{1-4} alkylene, or (aromatic C_{1-5} heterocyclyl)C_{1-4} alkylene, and
(4) OL_1Q wherein L_1 is C_{2-3} alkylene.

24. (Cancelled) A compound of claim 23, wherein G is selected from:
(5) formula (i) wherein L_4 and L_5 are each C_2 alkylene,
(6) formula (iii) wherein each of L_6 and L_7 is C_2 alkylene, and
(7) L_2Q wherein L_2 is methylene.

25. (Cancelled) A compound of claim 24, wherein G is L_2Q.

26. (Cancelled) A compound of claim 23, wherein R_{10} is H, branched C_{3-6} alkyl, or benzyl.

27. (Cancelled) A compound of claim 26, wherein R_{10} is isopropyl or benzyl.

28. (Cancelled) A compound of claim 23, wherein Q is a non-aromatic C_{2-5} heterocyclyl.

29. (Cancelled) A compound of claim 28, wherein Q is selected from piperidyl, N-(C_{1-6} alkyl)piperazinyl, piperazinyl, pyrrolinyl, pyrrolidinyl, and morpholinyl.

30. (Cancelled) A compound of claim 24, wherein Q is a non-aromatic C_{2-5} heterocyclyl.

31. (Cancelled) A compound of claim 30, wherein Q is selected from piperidyl, N-(C_{1-6} alkyl)piperazinyl, piperazinyl, pyrrolinyl, pyrrolidinyl, and morpholinyl.

32. (Cancelled) A compound of claim 25, wherein Q is selected from piperidyl, N-(C_{1-6} alkyl)piperazinyl, piperazinyl, pyrrolinyl, pyrrolidinyl, and morpholinyl.

33. (Amended) A compound of claim [23] 1, wherein R_5 is C_{1-5} alkyl, C_{3-4} alkenyl, C_{3-6} cycloalkyl, (C_{3-6} cycloalkyl) C_1alkylene, (phenyl)C_{1-3} alkylene, or (phenyl)C_{3-4} alkenylene.

34. (Cancelled) A compound of claim 23, wherein R_7 is hydroxyl, halo, or absent where one of L_6 and L_7 provides a double bond to the carbon atom to which R_6 and R_7 are attached.

35. (Cancelled) A compound of claim 1, wherein one of R_2 and R_3 is G.

36. (Amended) A compound of claim 1, wherein one of R_2 and R_3 is W [, and W is a heterocyclyl selected from: pyridyl, pyrimidyl, furyl, thiofuryl, imidazolyl, oxazolyl, thiazolyl, 2,3-dihydro-indolyl, benzimidazolyl, tetrazolyl, triazolyl, and pyrrolyl].

37. A compound of claim 21, wherein R_5 is branched C_{3-5} alkyl.

38. A compound of claim 21, wherein R_5 is isopropyl or cyclopentyl.

39. (Cancelled) A compound of claim 1, selected from 4-(4-Imidazol-1-yl-phenoxy)-1-isopropyl-piperidine, 4-(4-Imidazol-1-yl-phenoxy)-1-isobutyl-piperidine, 1-Isopropyl-4-(4-pyrrol-1-yl-phenoxy)-piperidine, and 5-Chloro-2-[4-(1-isopropyl-piperidin-4-yloxy)-phenyl]-1H-benzoimidazole.

40. (Cancelled) A compound of claim 39, selected from 4-(4-Imidazol-1-yl-phenoxy)-1-isopropyl-piperidine, 4-(4-Imidazol-1-yl-phenoxy)-1-isobutyl-piperidine, and 5-Chloro-2-[4-(1-isopropyl-piperidin-4-yloxy)-phenyl]-1H-benzoimidazole.

41. (Cancelled) A compound of claim 1, selected from [4-(1-Isopropyl-piperidin-4-yloxy)-phenyl]-phenyl-methanone, 4-(Biphenyl-4-yloxy)-1-isopropyl-piperidine, 4-(4-Benzyloxy-phenoxy)-1-isopropyl-piperidine, 1-Isopropyl-4-(4-phenoxy-phenoxy)-piperidine, 4-(4-Benzyl-phenoxy)-1-isopropyl-piperidine, [4-(1-Isopropyl-piperidin-4-yloxy)-phenyl]-phenyl-methanol, N-[4-(1-Isopropyl-piperidin-4-yloxy)-phenyl]-acetamide, 4-(4-Cyclopentyl-phenoxy)-1-isopropyl-piperidine, 4-(1-Cyclopentyl-piperidin-4-yloxy)-benzonitrile, 4-(1-Cyclobutyl-piperidin-4-yloxy)-benzonitrile, 4-(1-sec-Butyl-piperidin-4-yloxy)-benzonitrile, 4-(1-Isopropyl-piperidin-4-yloxy)-benzaldehyde, 4-(1-Cyclohexyl-piperidin-4-yloxy)-benzonitrile, 4-(1-Isopropyl-piperidin-4-yloxy)-benzonitrile, 4-(1-Cyclopropylmethyl-piperidin-4-yloxy)-benzonitrile, and 4-(1-Isobutyl-piperidin-4-yloxy)-benzonitrile, 4-(1-Propyl-piperidin-4-yloxy)-benzonitrile.

42. (Cancelled) A compound of claim 1, selected from 4-(Biphenyl-4-yloxy)-1-isopropyl-piperidine, 4-(4-Benzyloxy-phenoxy)-1-isopropyl-piperidine, 4-(4-Benzyl-phenoxy)-1-isopropyl-piperidine, 1-Isopropyl-4-(4-phenoxy-phenoxy)-piperidine, and N-[4-(1-Isopropyl-piperidin-4-yloxy)-phenyl]-acetamide.

43. A compound of claim 1, selected from 1-Isopropyl-4-[4-(1-isopropyl-piperidin-4-yloxy)-phenyl]-piperazine, 1-[4-(1-Isopropyl-piperidin-4-yloxy)-phenyl]-piperazine, and 1-[4-(1-Isopropyl-piperidin-4-yloxy)-phenyl]-piperazine.

44. (Amended to delete all compounds except the bolded compounds) A compound of claim 1, selected from 1-[4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-piperidine, **4-[4-(1-sec-Butyl-piperidin-4-yloxy)-benzyl]-morpholine,** 1-[4-(1-Cyclopentyl-piperidin-4-yloxy)-benzyl]-piperidine, 1-[4-(1-Isobutyl-piperidin-4-yloxy)-benzyl]-piperidine, 1-N-Isopropyl-4-{4-[5-(1-isopropyl-piperidin-4-ylsulfanyl)-tetrazol-1-yl]-phenoxy}-piperidine, {1-[4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-piperidin-4-yl}-methanol, 1-[4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-4-methyl-[1,4]diazepane, 1-[4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-azepane, 1-[4-(1-Isobutyl-piperidin-4-yloxy)-benzyl]-piperidine, 1-[4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-piperidin-4-ol, [4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-methyl-(1-methyl-piperidin-4-yl)-amine, 1-[4-(1-isopropyl-piperidin-4-yloxy)-benzyl]-4-benzyl-piperidine, N-[4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-N,N',N'-trimethyl-ethane-1,2-diamine, **1-[4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-4-methyl-piperazine,** Cyclohexyl-[4-(1-isopropyl-piperidin-4-yloxy)-benzyl]-methyl-amine, Butyl-[4-(1-isopropyl-piperidin-4-yloxy)-benzyl]-methyl-amine, 4-[4-(1-Cyclopentyl-piperidin-4-yloxy)-benzyl]-morpholine, 1-Isopropyl-4-(4-pyrrolidin-1-ylmethyl-phenoxy)-piperidine, Diethyl-[4-(1-isopropyl-piperidin-4-yloxy)-benzyl]-amine, **4-[4-(1-sec-Butyl-piperidin-4-**

yloxy)-benzyl]-morpholine, 1-[4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-4-phenyl-piperazine, 1-Benzyl-4-[4-(1-isopropyl-piperidin-4-yloxy)-benzyl]-piperazine, 4-[4-(4-Benzylidene-piperidin-1-ylmethyl)-phenoxy]-1-isopropyl-piperidine, **4-[4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-morpholine,** [4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-dimethyl-amine, **4-[4-(1-Cyclohexyl-piperidin-4-yloxy)-benzyl]-morpholine, 4-[4-(1-Isobutyl-piperidin-4-yloxy)-benzyl]-morpholine, 4-[4-(1-Propyl-piperidin-4-yloxy)-benzyl]-morpholine,** 1-[4-(1-Cyclohexyl-piperidin-4-yloxy)-benzyl]-piperidine, 1-[4-(1-Benzyl-piperidin-4-yloxy)-benzyl]-piperidine, 1-[4-(1-Cyclohexylmethyl-piperidin-4-yloxy)-benzyl]-piperidine, and 4-[4-(4-Piperidin-1-ylmethyl-phenoxy)-piperidin-1-yl]-butan-2-one.

45. (Amended to delete all compounds except the bolded ones) A compound of claim 1, selected from 1-[4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-piperidine, **4-[4-(1-sec-Butyl-piperidin-4-yloxy)-benzyl]-morpholine,** 1-[4-(1-Cyclopentyl-piperidin-4-yloxy)-benzyl]-piperidine, 1-[4-(1-Isobutyl-piperidin-4-yloxy)-benzyl]-piperidine, 1-N-Isopropyl-4-{4-[5-(1-isopropyl-piperidin-4-ylsulfanyl)-tetrazol-1-yl]-phenoxy}-piperidine, {1-[4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-piperidin-4-yl}-methanol, 1-[4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-4-methyl-[1,4]diazepane, 1-[4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-azepane, 1-[4-(1-Isobutyl-piperidin-4-yloxy)-benzyl]-piperidine, 1-[4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-piperidin-4-ol, [4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-methyl-(1-methyl-piperidin-4-yl)-amine, 1-[4-(1-isopropyl-piperidin-4-yloxy)-benzyl]-4-benzyl-piperidine, N-[4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-N,N',N'-trimethyl-ethane-1,2-diamine, **1-[4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-4-methyl-piperazine,** Cyclohexyl-[4-(1-isopropyl-piperidin-4-yloxy)-benzyl]-methyl-amine, Butyl-[4-(1-isopropyl-piperidin-4-yloxy)-benzyl]-methyl-amine, **4-[4-(1-Cyclopentyl-piperidin-4-yloxy)-benzyl]-morpholine**, 1-Isopropyl-4-(4-pyrrolidin-1-ylmethyl-phenoxy)-piperidine, Diethyl-[4-(1-isopropyl-piperidin-4-yloxy)-benzyl]-amine, **4-[4-(1-sec-Butyl-piperidin-4-yloxy)-benzyl]-morpholine, 1-[4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-4-phenyl-piperazine, 1-Benzyl-4-[4-(1-isopropyl-piperidin-4-yloxy)-benzyl]-piperazine,** 4-[4-(4-Benzylidene-piperidin-1-ylmethyl)-phenoxy]-1-isopropyl-piperidine, **4-[4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-morpholine,** [4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-dimethyl-amine, **4-[4-(1-Cyclohexyl-piperidin-4-yloxy)-benzyl]-morpholine, and 4-[4-(1-Isobutyl-piperidin-4-yloxy)-benzyl]-morpholine**.

46. (Cancelled) A compound of claim 1, selected from Cyclopropyl-[4-(1-isopropyl-piperidin-4-yloxy)-benzyl]-amine, [4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-(5-methyl-pyridin-2-yl)-amine, [4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-pyridin-2-yl-amine, [4-(1-Isopropyl-piperidin-4-yloxy)-

benzyl]-phenyl-amine, and (5-Chloro-pyridin-2-yl)-[4-(1-isopropyl-piperidin-4-yloxy)-benzyl]-amine.

47. (Amended) A compound of claim 1 or [23] 21, isotopically labelled to be detectable by PET or SPECT.

48. A pharmaceutical composition, comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

49. (Amended) A method of inhibiting histamine H_3 receptor activity in a subject, comprising administering an effective amount of a compound of claim 1, 21[23], 43, 45, or [46] to a subject in need of such inhibition of histamine H_3 receptor activity.

50. (Amended) A method of treating a subject having a disease or condition modulated by histamine H_3 receptor activity, comprising administering to the subject a therapeutically effective amount of a compound of claim 1, [23] 21, 43, 45, or [46].

51. (Amended) A method of claim 50, wherein said disease or condition is selected from the group consisting of sleep/wake disorders, arousal/vigilance disorders, migraine, asthma, dementia, mild cognitive impairment [(pre-dementia)], Alzheimer's disease, epilepsy, narcolepsy, eating disorders, motion sickness, vertigo, attention deficit hyperactivity disorders, learning disorders, memory retention disorders, schizophrenia, nasal congestion, allergic rhinitis, and upper airway allergic response.

52. (Cancelled) A method for treating a disease or condition modulated by at least one receptor selected from the histamine H_1 receptor and the histamine H_3 receptor, said method comprising (a) administering to a subject a jointly effective amount of a histamine H_1 receptor antagonist compound, and (b) administering to the subject a jointly effective amount of a compound of claim 1, 23, 45, or 46, said method providing a jointly therapeutically effective amount of said compounds.

53. (Cancelled) The method of claim 52 wherein the histamine H_1 receptor antagonist and the compound of claim 1, 23, 45, or 46 are present in the same dosage form.

54. (Cancelled) A method for treating diseases or conditions modulated by at least one receptor selected from the histamine H_2 receptor and the histamine H_3 receptor in a subject, comprising (a) administering to the subject a jointly effective amount of a histamine H_2 receptor antagonist compound, and (b) administering to the subject a jointly effective amount

of a compound of claim 1, 26, 27, or 41, said method providing a jointly therapeutically effective amount of said compounds.

55. (Cancelled) The method of claim 54 wherein the histamine H_2 receptor antagonist and the compound of claim 1, 23, 45, or 46 are present in the same dosage form.

56. (Amended) A method for treating one or more disorders or conditions selected from the group consisting of sleep/wake disorders, narcolepsy, and arousal/vigilance disorders, comprising administering to a subject a therapeutically effective amount of a compound of claim 1, [23] 21, 45,[or 46].

57. (Amended) A method for treating attention deficit hyperactivity disorders (ADHD), comprising administering to a subject a therapeutically effective amount of a compound of claim 1, [23] 21, or 45[, or 46].

58. (Amended) A method for treating one or more disorders or conditions selected from the group consisting of dementia, mild cognitive impairment [(pre-dementia)], cognitive dysfunction, schizophrenia, depression, manic disorders, bipolar disorders, and learning and memory disorders, comprising administering to a subject a therapeutically effective amount of a compound of claim 1, [23] 21, or 45[, or 46].

59. (Amended) A method for treating or preventing upper airway allergic response, nasal congestion, or allergic rhinitis, comprising administering to a subject a therapeutically effective amount of a compound of claim 1, [23] 21, or 45[, or 46].

60. (Cancelled) A method for studying disorders mediated by the histamine H_3 receptor, comprising using an ^{18}F-labeled compound of claim 1 or 23 as a positron emission tomography (PET) molecular probe.